ART. IV.—*On Phosphorus Poisoning and Fatty Degeneration.*—By WM. PEPPER, M.D. (Published by direction of the Biological and Microscopical Section of the Academy of Natural Sciences of Philadelphia.)

I ASK the attention of the Section to a few observations relative to the action of phosphorus upon the animal economy; and as the subject is closely connected with the question of fatty degeneration, I will premise a brief description of this latter process.

As we now employ the term fatty degeneration, it embraces all the conditions in which an excess of fat occurs in any organ, and consequently includes what is more accurately called fatty accumulation, as well as true fatty degeneration. The difference between these two conditions is, however, marked, and may be expressed somewhat as follows: that in fatty accumulation the particles of fat aggregate themselves between the cells of a part, or even within them, without any tendency to destroy them; while in the other form the increase of fat coincides with a loss of vital power of the cell, a degradation of its structure, and a tendency to disintegration. We find, as was most clearly pointed out by Virchow, physiological types of both of these processes in the animal body. Thus the marked increase of fat in the villi of the intestine, and ultimately in the hepatic cells, which follows the ingestion of fatty food, is a true instance of fatty accumulation, since the oily particles disappear after a time, and the parts regain their normal appearance; while, on the other hand, the secretion of milk is an illustration of true fatty degeneration, the epithelium of the lactiferous tubes undergoing a conversion into fatty molecules.

Apart, however, from these physiological instances, we meet with both of these forms in pathological processes, and I would call attention to the conditions under which they occur.

The first point which will appear from a review of these causes is that they all tend to produce a reduction in the vital force of the part or the individual, and are, so to speak, depressing in their character. So far as we are aware, the first requisite for a proper transformation of the fatty matters which enter the system, as well as for the normal retrograde changes in the nitrogenized elements of the tissues, is a full supply of oxygen, and we will therefore note that in all these conditions there is this one common feature of deficient supply of oxygen, or suboxidization. We may thus enumerate these conditions as:—

Firstly. When an excess of fat food, or of food capable of being converted into fat, is taken into the body, the amount of oxygen remaining at the ordinary figure. Here the oxygen is, of course, insufficient to oxidize the excess of fatty matter, and a tendency to fatty accumulation occurs.

Secondly. When the supply of oxygen becomes deficient to oxidize the fatty material, which, however, is not in excess. These conditions are met with in old age, where the amount of air inspired falls below the previous standard; they also occur in some diseases of the lungs; and finally, it is partly owing to this cause that the prolonged use of alcohol induces fatty degeneration. Here, again, it is manifest that the increase in amount of fat will be rather of the nature of an accumulation.

Thirdly. When the supply of oxygen is not sufficient to properly oxidize the nitrogenous elements of the tissues. In this case there is a retrograde change in the composition of the tissues, and the nitrogenous substances disappear to be replaced by fatty matter. It is evident that this can occur in two ways—either by replacement of the nitrogenous elements, which are removed in the ordinary waste of the body, by fat, or by a direct conversion of the nitrogenous substances into fat, instead of into urea, carbonic acid, and water. This last process, which is constantly witnessed in dead animal matter outside of the body when immersed in water, as in the experiments of Quain and Handfield Jones, is not acknowledged by some authorities as occurring in the living body. We believe, however, that it cannot be so excluded, since there are circumstances under which portions of the living body come to occupy very much the relation of dead tissue to the rest of the economy. There is a theory which has, however, been advanced, especially by Ranvier, to meet this difficulty, based upon the well-known fact that nearly all the tissues of the body contain varying amounts of fat, which in many instances is so combined with the albuminoid elements as not to assume its characteristic form, and be recognizable by the microscope. It is thus with the red blood-globules which contain a notable proportion of fatty matter, and with the brain, which contains the largest amount of combined fat of any tissue of the body. According to this view, then, when the nutrition of the cells of any part is impaired, the combination in which the fat exists is broken up, and it appears isolated and free to assume its ordinary form. The causes which give rise to this deficiency of oxygen are chiefly such as reduce the amount of blood reaching the part; alterations in the vessels, as atheroma of the larger arteries, or thickening of the capillary walls; embolism; deficient cardiac force, and destruction of the red blood-globules, the oxygen carriers of the blood, as in violent fevers, or in poisoning by certain substances. It is important to bear this fact in mind.

Fourthly. We recognize inflammation as a cause of fatty degeneration; though it probably acts in an indirect way. Thus the inflammatory products may so compress the bloodvessels passing through them that some neighboring part shall have its supply cut off and become fatty; or the imperfectly organized and poorly nourished inflammatory products, resulting from the too rapid proliferation of cells, formed in the meshes of the tissues, may themselves, and are indeed especially prone to, undergo fatty degeneration. It also appears, however, as in cases of death from acute inflammation of the pericardium, that the inflammatory stimulus causes a rapid increase of cell-action in the adjoining layer of tissue, under which the cells receive a larger amount of nutriment than can be properly oxidized, and thus come to present a fatty condition.

Local fatty degeneration may be due to one or all of these causes, and it may, moreover, happen that fatty accumulation may result from obstruction of the lacteal current from an organ, as the liver, so that the fatty chyle is dammed up in its cells. The view has also been advanced by Ranvier in regard to certain toxic substances, that they produce fatty degeneration by a peculiar depressing action upon the nutrition of the part, which favours the separation of the combined fat. These are, however, I believe, all the well-established causes of either fatty accumulation or fatty degeneration. It is not necessary to allude to the microscopical appearances of the different tissues in a state of fatty change, except to mention the fact that it is not always easy to distinguish whether it be due to accumulation or degeneration, whether it be a fragment of *paté de foie gras*, or of a liver in a case of yellow fever. In some cases of accumulation, however, we are able, by treating the cells with ether, to remove the fat and obtain a view of the cell with its investing membrane and nucleus intact; while, on the other hand, in cases of marked degeneration, there usually will be evidence of more or less destruction of the cells, which appear shrivelled, irregular, and without nuclei. Again, tissues in the state of fatty change of whichever form, present many external characters alike. They are softened and flabby, opaque and often of a yellowish tinge, of low specific gravity, so as to even float in water. But, as would be expected in cases of true accumulation, the organ may even increase in size; while, in extreme degeneration, it is often much reduced below the normal dimensions.

Having premised this about the conditions under which fatty change occurs, I will now offer a few observations on the effects of phosphorus upon the animal economy.

The following case of phosphorus poisoning in a human being is condensed from Dr. Bence Jones, as quoted from Rokitansky:—

A girl poisoned herself by phosphorus matches. Jaundice appeared in a day or two; soon after, she became wandering, vomited a dark brown matter and had convulsions; and on the sixth day died.

At *autopsy*, the body was well nourished; skin yellow; membranes and brain bloodless. In the throat, bloody, frothy, very tough mucus. In the pleuræ, mediastinum, and over base of heart ecchymoses in some places of considerable extent; a slight pleuritic effusion on left side. Lungs full of blood. Liver very fatty, pale yellowish-red, pasty and empty of blood. In the gall-bladder and gall ducts, slimy mucus. Mucous membrane of the stomach swollen, and containing a brown, thick fluid. Small intestines contained semi-fluid matter mixed with blood; spleen small and friable. Kidneys large, very light yellowish-white, and slightly jaundiced; the epithelium of the tubes of the cortical structure was distended with small and large fat cells, and the tubes themselves were full of fat.

Exp't 1. *Sept.* 17. A very healthy, light-gray rabbit had 1 gr. of phosphorus dissolved in fʒj olive oil injected into the rectum. For two days it seemed to eat quite well, drank but moderately, and died on evening of third day.

Autopsy fifteen hours after death.—Marked rigor mortis. The stomach was much distended with quite dry finely-chewed grass; the mucous membrane whitish and quite healthy; there was, however, one small patch of congestion; small intestine empty and contracted; cæcum distended with material much like contents of stomach; rectum and descending colon empty, slightly discolored, no ulceration; liver of full size, apparently slightly soft, pale yellowish colour. On microscopic examination, cells literally stuffed with large oil drops, a good deal of free oil also, and in places, evidences of cells breaking down; spleen small, dark, not examined microscopically; kidneys, presented some congestion of their medullary portion, but cortical portion pale, and on microscopic examination epithelium highly granular and fatty; tubes opaque, and with granular contents. No signs of peritonitis. Heart of normal size; contained very little blood; tissue not materially softened; on microscopic examination presented distinct granular change, with some free oil; voluntary muscles very pale, but showed no change of structure.

Exp't 2. *Sept.* 2. About 1 grain of phosphorus in a mixture of ʒj flour, syrup and glycerin was given by the mouth to a second healthy dark-gray rabbit. It appeared to suffer much soon after its introduction, but revived, ate quite well for two days; became very ill, emaciated, with haggard appearance, hurried breathing; and died on sixth day.

Autopsy five hours after death.—Rigor mortis moderate. *Stomach* not so much distended as in previous case; pyloric extremity healthy, but fundus discoloured and so much softened and thinned that it ruptured in trying to remove it. *Liver* of full size, soft and fatty, of putty colour, with little blood escaping on section; cells all gorged with fat drops and molecules; here and there nuclei visible, but usually absent or totally obscured; a good deal of free oil, and apparent disintegration of the cells in places. *Kidneys* soft, pale; epithelium granular; tubules opaque, and in places some oil drops noticed. *Spleen* small and very soft. *Heart* distended with dark clots on right side, and containing a good deal of dark fluid blood in left cavities. The microscope showed free oil drops in the blood; the corpuscles pale; the fibrin coagulated firmly; the fibrils of the heart were decidedly granular, though in places transverse striation was visible, and but little free oil was noticed; voluntary muscles healthy.

Exp't 3. A healthy white rabbit was killed suddenly by a blow on back of neck, after being kept in a box by the side of the last rabbit, and fed upon similar food during the course of the experiment.

Autopsy half hour afterwards.—*Stomach* healthy, distended with grass; cæcum also distended; rest of bowel contracted. *Liver* of yellowish colour, firm; under microscope, cells presented a good many fatty particles, but few oil drops, and little free oil; and in a great many instances the nuclei could be observed. *Kidney* quite firm, epithelium pale, and some of the tubes slightly granular, no free oil. *Spleen* double the size of that in previous cases and more firm. *Heart* contained a little fluid blood and small dark clots, was quite firmly contracted; fibrils were, however, almost, if not quite, as granular as in previous case; blood contained no fatty particles; voluntary muscles healthy.

In summing up the results of these three observations, it is to be borne in mind that even in the healthy rabbit, the hepatic cells contained a notable amount of fat, and the muscular fibrils of the heart were distinctly granular; and I learn from my friend Dr. S. Weir Mitchell, whose extensive researches in experimental physiology are so well known, that it has frequently happened to him to find marked fatty accumulation in the tissues of healthy rabbits. There was, however, no difficulty in deciding that, in the case of the rabbits to whom phosphorus had been administered, the fatty condition of the organs was altogether morbid. The marked softness and friability of the tissues indicated this, as well as the microscopic appearances, which showed a very much greater amount of free oil as well as of fat contained in the cells, and in addition positive evidences of disintegration of the cells of the liver at least. It is, however, important to bear in mind, in all experiments upon the production of fatty degeneration, that many of the lower animals appear to present a fatty state of the muscles and glandular organs as an habitual and normal condition. Handfield Jones has noticed this in regard to London dogs and cats; and Ranvier disclosed the fallaciousness of an entire series of experiments on phosphorus poisoning in frogs, by showing that the tissues of these animals are naturally fatty at certain periods of the year.

Finally I will quote from Ranvier's memoir on phosphorus poisoning (*Mém. de la Société de Biologié*, 1866), the following observation on the local action of phosphorus:—

> "The 24th of September, a piece of phosphorus seven millimetres long and two millimetres thick, was introduced into the subcutaneous tissue of a young rabbit, between the ears. The calcaneum of a new-born rabbit was then introduced into the right flank of the first animal. Between this time and the 4th of October, evidences of inflammation were observed in the neighbourhood of the calcaneum, whilst no such signs were noticed near the fragment of phosphorus. On this latter date, the animal was killed, and the calcaneum was found surrounded by a layer of organizing inflammatory lymph, while nothing of the kind was present in the neighbourhood of the phosphorus, which preserved its transparency, and had not appreciably diminished in volume.
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> There was no fatty degeneration of the liver, kidneys, or muscles.

The same observer introduced into the subcutaneous tissue of different rabbits, various inert foreign bodies, and constantly found that in the course of a few days they induced suppurative inflammation.

It is not necessary to spend time in illustrating further the fact that in cases of phosphorus-poisoning acute and extreme fatty degeneration does occur. In addition to the innumerable experiments that have been performed on the lower animals by German and French observers, Tardieu (*Etude Médico-Légale sur l'Empoisonnement*, 1867) has succeeded in collecting no less than twenty-three cases of poisoning by this substance in the human subject; and in his admirable description of the lesions found in the cases there is conclusive evidence of every grade of fatty change, from a condition in which the cells retain their size and shape, but are partly filled with fine fatty granulations which conceal the nucleus, to the most advanced stage in which the cell becomes disintegrated and the fat set free.

I may, however, allude to the astounding rapidity with which this change occurs, since Tardieu narrates cases in which, within so short a time as forty-eight hours, fatty degeneration of the heart, liver, kidneys, glands of the stomach, and voluntary muscles has occurred. It is impossible to avoid observing the analogy which the symptoms in these cases present to those of yellow fever and acute yellow atrophy of the liver, in all of which the constant vomiting, frequently of blood matters; the jaundice; the condition of the urine, which is often albuminous or even bloody; the uncertain and frequently low grade of the febrile action; the character of the nervous symptoms; and, finally, the post-mortem conditions—the universal fatty degeneration of the tissues, the ecchymoses of the serous investments of the different organs, the altered state of the blood—are so prominent. The relation between these three conditions offers, indeed, one of the most attractive and important pathological problems of the present day.

It remains, however, to endeavour to determine what is the particular method by which phosphorus produces these effects, and we will find that various theories have been already advanced. Bearing in mind the conditions we have already enumerated under which fatty degeneration occurs, it is at once evident that the action of phosphorus has no relation whatever to the amount of fatty food taken during the time of its activity.

There remain, then, but four views—namely, that phosphorus checks the action of the lacteals; that it has a specific depressing action on cell-nutrition; that it induces fatty degeneration by its irritant action; and, finally, that it acts upon the blood, destroying the red globules, and thus preventing sufficient oxygen being carried to the nitrogenous tissues.

The idea that phosphorus induced fatty degeneration by arresting the absorption of fat by the chyliferous vessels was originated by Lewin at a time when it was not known that any other organ than the liver was affected in phosphorus poisoning, and accorded with the observation that in animals who had taken phosphoretted oil, and had been killed a few hours after, the chyliferous vessels were found filled with serous liquid merely, while the blood in the portal vein contained abundant fine fatty particles, which he supposed to be filtered out by the liver. Since the observation, however, that in such cases all tissues alike suffer from the effects of the poison, it is manifest that it must act in some other manner.

The next theory is that propounded by Ranvier, that phosphorus determines fatty degeneration by impairing the nutrition of the histological elements, in virtue of its contra-stimulant action on them, and thus destroys the combination which had existed between the fatty and albuminoid matters. One of the arguments which he adduces in support of this view is the absence of any local irritant action of phosphorus, as detailed in the case I have already related. He has performed the same experiment of placing a piece of phosphorus under the skin upon several frogs, and has found in none of them any traces of inflammation around the piece of phosphorus, while, in several cases, death followed at long intervals, and the viscera were found highly fatty.

These observations upon the local action of phosphorus are highly interesting, and deserve to be carefully prosecuted. They do not, however, appear to me conclusive in regard to the mode of production of fatty degeneration, since it was not found that the parts immediately in contact with the fragment were especially affected. And again, though it is thought by many that phosphorus may, to a certain extent, be absorbed as such, and retained in an unchanged condition in the viscera, as shown by a case in which the viscera of a woman who died while taking phosphorus medicinally, were found luminous, free phosphorus can scarcely ever be detected, after death, in the tissues; and the probability is very strong that it is almost entirely oxidized, and passes through the economy as phosphoric acid.

Munk and Leyden have also found by experiment that if a solution of phosphorus be injected directly into the blood, phosphorous acid vapours are exhaled, and pneumonia set up, but no fatty degeneration occurs. In like manner, phosphoretted hydrogen and hypophosphorous acid were tried without producing the characteristic lesions. But when, on the other hand, phosphoric acid was introduced either into the blood or stomach, extreme fatty degeneration was quickly produced. It appears, therefore, that though phosphorus is, according to Ranvier's experiments, singularly inert and unirritating, it is not in virtue of this quality that fatty degeneration is induced by poisonous doses of it, since it appears necessary for it to undergo oxidation into phosphoric acid in order to produce this effect.

I have already alluded to the fact that Virchow and his school explain the production of fatty degeneration in phosphorus poisoning by the irritant action of this substance, which induces rapid proliferation of cells, and ultimately fatty change in the parts. Ranvier, who indeed holds that inflammation and fatty degeneration are antagonistic, calls attention to the undoubted fact that it is by no means invariable to have evidences of gastro-intestinal inflammation, and that for such to be present it is not necessary that the poison should have been introduced into the stomach.

When, however phosphoric acid itself is injected into the stomach, it produces the strongest marks of corrosion, and the probability is that when phosphorus is used the result depends upon the rapidity with which it becomes oxidized and is excreted from the system, since in quite a large proportion of cases decided congestion, tumefaction, and even inflammation have been noted after death.

It appears to us, then, that phosphorus acts as so many other poisons do, by entering the blood in the form of a highly irritant substance, and in the course of its excretion from the various glands, induces a degree of irritation bordering on inflammation, attended with a proliferation of cells, which, as frequently happens, are not fully organized, and readily undergo fatty degeneration.

There is, however, one further point in the action of phosphoric acid which must strongly favour the occurrence of this change, and which, indeed, has been assigned by Munk and Leyden as the sole cause of it—I refer to its action on the red blood-globules, which, as shown by these observers, are dissolved by it as by the bile acids. The falling of the temperature of the blood, the ecchymoses of the serous membranes, the serous effusions stained with dissolved hematine, the bloody urine, which are noted after its introduction, are all results of the same peculiar action.

The manner in which this destruction of the red globules, which are the oxygen-carriers of the blood, favours fatty degeneration, is evident; and, when combined with the tendency which always exists in cells formed by unduly active proliferation, to undergo this change, appears to me to afford a satisfactory solution of the extraordinary lesions met with in phosphorus poisoning.

I may add that the authors just referred to have extended their experiments to sulphuric, nitric, oxalic, and tartaric acids, and have shown that all substances which dissolve or destroy the blood globules tend to produce fatty degeneration of the various tissues.

It may not, in conclusion, be amiss to again allude to the strangely close similarity between the symptoms of yellow fever and acute atrophy of liver, and those of poisoning by phosphoric acid, taken in connection with the fact that the bile acids resemble it closely in their action on the blood.

ART. V.—*Sources of Error in the Analysis of Urine.* By M. C. LEA and WALTER F. ATLEE, M. D.

OUR attention has been recently attracted to two sources of error in urine analysis. As these are such as may very easily take place, and may lead to very serious errors in treatment, it has seemed desirable to call attention to them. The one source of error leads to an *under-estimation of the quantity of uric acid*, the other to an *illusory detection of fat.* In this last the illusion may be such as to deceive inexperienced observers,